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EXAMINER	
MACFARLANE, STACEY NEE	
ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/525,266	ONG ET AL.	
	Examiner	Art Unit	
	STACEY MACFARLANE	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *03 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,26 and 29-32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,26 and 29-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *3/3/2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on march 3, 2009 has been entered.

Response to Amendment

2. Claims 1, 2, 3 and 26 have been amended, claims 27 and 28 cancelled, and claims 29-32 have been newly added as requested in the amendment filed on March 3, 2009. Following the amendment, claims 1-3, 6, 26 and 29-32 are pending in the instant application and are under examination in the instant office action.

3. Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

4. Applicant's arguments filed on March 3, 2009 have been fully considered but they are not deemed to be persuasive for the reasons set forth below.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. As currently amended, Claims 1-3, 6, 26 and 29-31 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6. Claims 1-3, 6, 26 and 29-31 are vague and indefinite in their recitation of administration "wherein said administration is carried out under conditions effective to ...". One of ordinary skill in the art would not be reasonably apprised as to the scope of those required conditions and neither the claims themselves nor the specification explicitly define the requisite conditions. Therefore, the metes and bounds of the method of the invention are unclear.

On page 4 of Remarks filed March 3, 2009, Applicant traverses the rejection on the grounds that the amendments to the claims "to recite that the step of administering is carried out repeatedly" obviates the rejection. This is not found persuasive. Claims still recite that repeated administration "is carried out under conditions effective to treat or prevent". One of ordinary skill in the art may interpret the claims to encompasses or even require elements or other conditions that are not explicitly set forth. Therefore, there is no clear delineation of what the method encompasses, and the claims are indefinite. If the method does not encompass or require further "conditions", then eliminating the recitation would obviate the rejection. Examiner suggests claim language along the lines of "repeatedly administering ...to a patient in need of such treatment, wherein said repeated administration is effective to treat or prevent atherosclerosis".

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. As currently amended, Claims 26 and 31-32 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement for reasons of record as applied to claims 26-28 in the previous Office action.

On pages 5-6 of Remarks filed March 3, 2009, Applicant traverses the rejection. As amended claims recite the following genera of active agents: "a CD36 ligand that reduces uptake of oxidized low density lipoprotein (oxLDL)" (claim 26); and a Growth Hormone Releasing Peptide (GHRP) "wherein the GHRP does not induce secretion of growth hormone" (claims 31 and 32). Applicant submits that these genera are fully supported by the specification, which identifies GHRPs by citation to 18 prior art references (page 9, lines 5-15). Specifically, Applicant states: "In particular, the prior art identifies twelve GHRPs with GH releasing activity in WO 89/07110 and WO 89/07111; seventeen GHRPs with GH releasing activity in WO 93/04081; more than one hundred GHRP peptidomimetic compounds in WO 96/015148; twenty GHRPs with GH releasing activity in U.S. 4,411,890; and ten GHRPs that lack GH releasing activity in U.S. 6,025,471 (one of which is EP80317). Thus, the prior art demonstrates an association between the structure and function of these GHRPs." This is not found persuasive for the following reasons.

This citation within the specification describes GHRPs in general but the claims require GHRPs that fulfill requisite functions: namely "reduce uptake of oxidized low

density lipoprotein" and/or "does not induce secretion of growth hormone". Applicant's indication that there are species within the genus that do not fulfill these functions "twelve GHRPs with GH releasing activity in WO 89/07110 and WO 89/07111; seventeen GHRPs with GH releasing activity in WO 93/04081; more than one hundred GHRP peptidomimetic compounds in WO 96/015148; twenty GHRPs with GH releasing activity in U.S. 4,411,890" (Remarks page 6) further strengthens the reasons for rejection. It is precisely because Applicant has not provided a partial or complete structure or other distinguishing feature of those species of the GHRP family that reduce uptake of oxidized low density lipoprotein and/or do not induce secretion of growth hormone, that the rejection is based. Applicant has not conveyed to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

The specification states: "GHRPs which consist of a family of small synthetic peptides modelled from Met-enkephalins, possess potent and dose depended growth hormone-releasing activity" (page 2, paragraph 3). However, the claims are drawn to a subset of molecules GHRPs that are further defined by the function of not inducing secretion of growth hormone (claims 31 and 32). From the specification, it is clear that Applicant is in possession of specific examples of GHRPs that fulfill this required activity, namely hexarelin and EP80317. The claims, however, encompass method of administration one or more GRHP, thus, the claims are not limited to specific molecules with known structure.

In order to provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof. In the instant case, the only factor present in the claim is a recitation of activity: reducing uptake of oxLDL and/or not inducing secretion of growth hormone. There is not even identification of any particular portion of the structure that must be conserved for said activity or activities. As stated above, it is not even clear what molecules except EP80317 are considered to be GRHPs that do not induce secretion of growth hormone. The specification specifically states:

> "GHRPs that may be mentioned include those of the hexarelin (HEX) family, such as HEX (His-(D)-(Me)Trp-Ala-Trp-(D)-Phe-Lys-NH.sub.2) and EP80317 (Haic-(D)-(Me)Trp-(D)-Lys-Trp-(D)-Phe-Lys-NH.sub.2), the latter peptide being devoid of GH-secreting activity in vivo. Preferred GHRPs include Hexarelin and EP80317. Particularly preferred GHRPs include those, like EP80317, that are devoid of GH-secreting activity in vivo".

The specification fails to provide the distinguishing feature(s) of a representative number of species for the recited genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description and possession of the claimed genus.

Adequate written description requires more than a mere recitation of activity as part of the invention and a reference to potential methods of isolating or screening molecules that have said activity. The compound itself is required. See *Fiers v Revel*, 25 USPQ2d 1601 at 1601 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. Therefore, the claims are rejected for lack of written description.

Claim Rejections - 35 USC § 112

9. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 1-3, 6, 26, and 29-32 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for prevention of the formation of atherosclerotic plaques in apolipoprotein E-deficient (apoE-/-) mice fed an atherogenic diet comprising administering EP80317, does not reasonably provide enablement for a method of treating or preventing atherosclerosis in *any* patient in general, any patient at risk of developing atherosclerotic plaques, or any patient already having atherosclerotic plaques, comprising the repeated administration of *any* one or more Growth Hormone Releasing Peptide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure would require undue experimentation include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art and, (8) the breadth of the claims. In re Wands, 8 USPQ2d, 1400 (CAFC 1988).

With respect to claim breadth, the standard under 35 U.S.C. §112, first paragraph, entails the determination of what the claims recite and what the claims mean as a whole. In addition, when analyzing the scope of enablement, the claims are analyzed with respect to the teachings of the specification and are to be given their broadest reasonable interpretation that is consistent with the specification. See MPEP 2111 [R-5], which states: During patent examination, the pending claims must be "given their broadest reasonable interpretation consistent with the specification." Phillips v. AWH Corp., 415 F.3d 1303, 75 USPQ2d 1321 (Fed. Cir. 2005). See also In re Hyatt, 211 F.3d 1367, 1372, 54 USPQ2d 1664, 1667 (Fed. Cir. 2000). Applicant always has the opportunity to amend the claims during prosecution, and broad interpretation by the examiner reduces the possibility that the claim, once issued, will be interpreted more broadly than is justified. In re Prater, 415 F.2d 1393, 1404-05, 162 USPQ 541, 550- 51 (CCPA 1969).

As such, Claim 1 broadly encompasses a method of treating or preventing atherosclerosis in any patient comprising repeatedly administering any GHRP. Firstly, it is well-recognized within the art that a variety of factors, both genetic and

environmental, contribute to the etiology of atherosclerosis. The method broadly encompasses the prophylaxis of atherosclerosis in the general population comprising repeatedly administering any GHRP, and as such broadly reads upon methods comprising repeatedly administering GHRPs to infants from birth with the effect of prevention of atherosclerosis, or successfully preventing atherosclerosis for developing in persons with significant risk factors such as smoking, high-fat diet, and genetic hyperlipidemia. Thus, the claims encompass prevention and treatment of all atherosclerosis, which is unreasonably broad. A skilled artisan would not know how to treat or prevent atherosclerosis in general based solely on the administration of any one or more GHRP.

As opposed to the claims, what is disclosed about the claimed method is narrow: The sole working example states:

> "A significant reduction of the lesion area by 31.3% and 39.2% was observed in the ApoE-null mice aorta following the daily treatment with EP80317 (300 µg/kg) for 6 and 8 weeks, respectively. In addition, a reduction of 36%, although not significant (due to larger variability in the control group), of the lesion area of ApoE-null aortas could be observed following the daily treatment with EP80317 (300 lxg/kg) for a period of 4 weeks as compared to controls treated with NaC1.
>
> No significant difference in terms of percentage of the lesion area in the aorta could be observed following the treatment with hexarelin (8%) for a period of 4 weeks as compared to controls treated with 0.9% NaC1."

Thus, the specification provides guidance only that treatment of EP80317 provides prevention of atherosclerotic aortic lesions in a mouse model for atherosclerosis. The specification, however, provides no direction or guidance as how the method comprising administering EP80317 is to be used for the treatment of existing atherosclerotic plaques, or for the prevention of atherosclerosis comprising the repeated administration of any other GHRP. In fact the specification teaches away from the method as performed by any GHRP by teaching that hexarelin has no significant effect. Therefore, the disclosure provides no guidance as to how to use the invention to the full extent of the scope claimed. Absent such guidance, one of ordinary skill in the art would need to look to the state of the art at the time of filing to discover how to practice Applicant's invention, as currently claimed.

Although the state of the art at the time of filing recognized the an acute administration of a dose of hexarelin to a patient who has coronary artery disease during by-pass surgery and subsequent improved cardiac function (Broglio et al. 2002 cited in the Paper mailed 12/4/2007), there was nothing within the art to teach or suggest that repeated administration of any GHRP was successful to treat or prevention atherosclerosis in any patient. Thus, much unpredictability remained within the art with respect to the role of GHRPs in the etiology and pathology of athersclerosis in general. Absent such teachings within the art and barring specific guidance within the instant specification, one of ordinary skill in the art would have had to make a substantial inventive contribution in order to practice the method to the full scope of the claims.

The standard of an enabling disclosure is not the ability to make and test if the invention works but one of the ability to make and use with a reasonable expectation of success. A patent is granted for a completed invention, not the general suggestion of an idea and how that idea might be developed into the claimed invention. In the decision of Genentech, Inc, v. Novo Nordisk, 42 USPQ 2d 1001, (CAFC 1997), the court held that:

> "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable" and that "[t]ossing out the mere germ of an idea does not constitute enabling disclosure". The court further stated that "when there is no disclosure of any specific starting material or of any of the conditions under which a process is to be carried out, undue experimentation is required; there is a failure to meet the enablement requirements that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art", "[i]t is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement".

The instant specification is not enabling because one cannot follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. A skilled artisan would have had to first demonstrate that the repeated administration of any GHRP would be effective to prevent the formation of atherosclerotic plaques in any patient, and furthermore that said administration was successful to treat already developed atherosclerotic pathology. Such experimentation

goes beyond that which is considered to be "routine" within the art, and requires undue experimentation in order to bridge the gaps between effect in a specific animal model and clinically relevant application of the invention commensurate in scope with the claims.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 1 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Imbimbo (1994), for reasons of record in the previous Office Action.

On pages 7-9 of Remarks filed March 3, 2009, Applicant traverses the rejection on the following grounds. Applicant states that while Imbimbo teaches hexarelin administration to healthy male subjects in three intravenous doses. Applicant argues that because "all injections were separated by 'one-week washout periods' (see Imbimbo, study design) ...each does used in Imbimbo was effectively a single administration rather than repeated administration". Furthermore, Applicant traverses that "To assert that Imbimbo inherently anticipates the present invention, the PTO bears the burden of demonstrating that the male subjects of Imbimbo necessarily had a risk factor for atherosclerosis" (page 8 Remarks). This argument has been considered in full but is not found persuasive for the following reasons.

Firstly, it should be noted that Applicant's disclosure is not found to be enabling for a method comprising administration of hexarelin, however, because the scope of the independent claim is broad and comprises the sole active Step of repeated administration of *any* GRHP for the treatment or prophylaxis of atherosclerosis, or for the repeated administration of hexarelin, then the following art can be applied to claims 1 and 6.

Claims 1 and 6 are drawn to a method of treatment or prophylaxis of atherosclerosis comprising repeated administration to a patient one or more GHRP; wherein the one or more GHRP is hexarelin. Traverse with respect to the PTO's burden to necessarily demonstrate risk factors is moot, because the claims do not require such risk factor criteria for said patient, nor do they provide a requisite periodicity upon the repeated administration. The instant claims read upon a method of prophylaxis of atherosclerosis comprising the sole active step of repeated administration of hexarelin with no limitation with respect to whom or how that repeated administration is achieved. One of ordinary skill in the art would recognize that the instant method fails to distinguish over the method of Imbimbo, in which hexarelin was administered 3 times ("repeatedly") to patients, thus resulting in prophylaxis of atherosclerosis. Thus, the method of the instant claims is anticipated by the method of the prior art and the claims are rejected.

Conclusion

13. No Claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to STACEY MACFARLANE whose telephone number is (571)270-3057. The examiner can normally be reached on M-W and ALT F 5:30 to 3:30, TELEWORK-Thursdays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Stacey MacFarlane
Examiner
Art Unit 1649

/John D. Ulm/
Primary Examiner, Art Unit 1649